CENTER FOR DRUG EVALUATION AND RESEARCH

74-890

APPLICATION NUMBER:

BIOEQUIVALENCE

SEP 26 1996

Cimetidine Tablets
ANDA # 74-890: 200, 300, 400 & 800mg
Reviewer: Hoainhon Nguyen
WP # 74890dw.996

TorPharm Inc.
Etobicoke, Canada
Submission Date:
September 5, 1996

Review of Dissolution Data and Waiver Request

The firm has submitted an amendment in response to the Division of Bioequivalence deficiency comment on its original submission dated April 19, 1996.

In the review of the original submission, the dissolution testing for all strengths of the test product was found unacceptable due to incorrect medium used: 0.1N H Cl instead of water as specified in the USP-23.

In the current amendment, the firm indicated that the reference to 0.1N H Cl as the dissolution medium in the summary report is "a typographical error". The applicable laboratory notebooks were audited by the firm and it was confirmed that water, not 0.1N H Cl, was actually used for the dissolution testing. A revised summary report is provided in this amendment.

Comment: The dissolution testing results are summarized below.

Drug (Generic Name):Cimetidine Tablets Firm: TorPharm Inc.
Dose Strength: 200, 300, 400 & 800 mg
ANDA # 74-890 Submission Date: April 19, 1996

Table - In-Vitro Dissolution Testing

Conditions for Dissolution Testing:
USP XXIII Basket X Paddle RPM 100 No. Units Tested: 12
Medium: Water Volume: 900 ml
Reference Drug: (Manuf.) Tagamet Tablet, 200, 300, 400 & 800 mg; SKB
Assay Method: _____

Results of In-Vitro Dissolution Testing:
Specifications:

Test Product Lot # 50043 Strength (mg) 800			Reference Product Lot # 804-4T27 Strength (mg) 800	
Sampling Time (Min.)	Mean % Dissol.	Range (CV%)	Mean % Dissol.	Range (CV%)
5	34	(7)	20	(34)
10	81	(5)	66	(7)
15	91	(4)	95	(3)
30	97	(2)	102	(1)

Test Product Lot # 50066 Strength (mg) 200			Reference Product Lot # 501-3T12 Strength (mg) 200	
Sampling Time (Min.)	Mean % Dissol.	Range (CV%)	Mean % Dissol.	Range (CV%)
10	102	(3)	99	(2)
15	100	(2)	100	(2)
30	100	(2)	101	(3)

Test Product Lot # 50067 Strength (mg) 300			Reference Product Lot # 74T13 Strength (mg) 300	
Sampling Time (Min.)	Mean % Dissol.	Range (CV%)	Mean % Dissol.	Range (CV%)
10	100	(2)	97	(2)
15	101	(2)	98	(2)
30	101	(2)	99	(2)

Test Product Lot # 50071 Strength (mg) 400			Reference Product Lot # 7294T26 Strength (mg) 400	
Sampling Time (Min.)	Mean % Dissol.	Range (CV%)	Mean % Dissol.	Range (CV%)
10	97	(3)	78	(8)
15	98	(2)	94	(1)
30	98	(2)	98	(1)

Comments:

1. The dissolution data for the test product are acceptable.

2. The single-dose fasting and fed bioequivalence studies for the 800 mg strength demonstrate that the test and reference products are equivalent in their rate and extent of absorption as measured by lnCMAX, lnAUC (0-T) and lnAUC (0-Infinity) of Cimetidine. (See review of submission dated April 19, 1996)

3. Comparative formulations given for 200 mg, 300 mg, 400 mg and 800 mg show that three lower strengths are proportionally similar to the 800 mg. (See review of submission dated April 19, 1996)

Recommendations:

1. The dissolution testing conducted by TorPharm Inc. on its Cimetidine Tablets, 200 mg, lot # 50066, 300 mg, lot # 50067, 400 mg, lot # 50071, and 800 mg, lot #50043, and Tagamet Tablets, 200 mg, lot # 5013T12, 300 mg, lot # 74T13, 400 mg, lot # 7294T26 and 800 mg, lot # 8044T27, is acceptable.

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP XXIII apparatus I (basket) at 100 rpm. The test product should meet the following specification:

[redacted]

2. The single-dose fasting and fed bioequivalence studies conducted by TorPharm Inc. on the test product, Cimetidine Tablets, 800 mg, lot # 50043, comparing it with the reference product, Smith Kline Beecham's Tagamet^{R} Tablets, 800 mg, lot # 8044T27, have been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product is bioequivalent to the reference product under fasting and fed conditions.

3. The firm has demonstrated that the formulation of its Cimetidine Tablets, USP, 200, 300 and 400 mg, are proportionally similar to the 800mg strength that underwent acceptable in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the 200, 300 and 400 mg tablets is granted. The firm's Cimedidine Tablets, 200, 300 and 400 mg, are therefore deemed bioequivalent to Tagamet[R] Tablets, 200, 300 and 400 mg, respectively, manufactured by SmithKline Beecham.

9-20-96

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 9/20/96

Concur: Date: 9/26/96

Keith Chan, Ph.D.
Director, Division of Bioequivalence

AUG 16 1996

Cimetidine Tablets
ANDA # 74-890: 200, 300, 400 & 800 mg
Reviewer: Hoainhon Nguyen
WP # 74890sdw.496

TorPharm Inc.
Etobicoke, Canada
Submission Date:
April 19, 1996

Review of Bioequivalence Studies, Dissolution Data and Waiver Requests

I. Background:

Cimetidine is a histamine H2-receptor antagonist, used for the treatment of endoscopically or radiographically confirmed duodenal ulcer, pathologic GI hypersecretory conditions (e.g., Zollinger-Ellison syndrome, systemic mastocytosis, and multiple endocrine adenomas), and active, benign, gastric ulcer.

Following intravenous administration, the plasma concentration profile follows multicompartmental characteristics. The total systemic clearance is high (500 to 600 ml/min) and is mainly determined by renal clearance. The volume of distribution is of the order of 1 L/kg. Elimination half-life is approximately 2 hours. Following oral administration of cimetidine, 2 plasma concentration peaks are frequently observed at about 1 hour and after about 3 hours, probably due to discontinuous absorption in the intestine or individual variation in gastric emptying (but not enterohepatic recycling since the biliary excretion rate in man is less than 2%). The absolute bioavailability is about 60% in healthy subjects and around 70% in peptic ulcer patients. Absorption and clearance of cimetidine are linear after 200 and 800 mg doses. When given with food, the extent of absorption of the drug remains unchanged but the time to reach the maximum peak concentration is delayed with only one peak in the plasma concentration curve observed at about 2 hours. Plasma protein binding of cimetidine is 20% and does not significantly affect the pharmacokinetics of the drug. Cimetidine distributes extensively into kidney, lung and muscle tissues, but less than 1% into the cerebrospinal fluid.

Following IV administration, about 50 to 80% of the dose is recovered in urine as unchanged cimetidine. This fraction is less after oral doses. Biliary excretion of

cimetidine accounts for about 2%. About 25-40% of the cimetidine dose is eliminated as metabolites, formed mainly in the liver. The metabolites are sulphoxide and 5-hydroxymethyl derivatives, and possibly guanylurea, although this latter compound may result from in-vitro degradation. According to the review article by A. Somogyi and R. Gugler ("Clinical Pharmacokinetics of Cimetidine". Clinical Pharmacokinetics 8: 463 - 495 (1983), hydroxymethyl metabolite accounted for 4.4 +/- 1.1% of the dose, cimetidine sulfoxide 7.4 +/- 1.3%, guanylurea metabolite 1.6 +/- 0.4% and a newly identified cimetidine-N'-glucuronide 24.0 +/- 4.9%. The glucuronide metabolite has not been tested for its activity, but the other metabolites have extremely weak histamine H2-antagonistic properties. Elimination of cimetidine is accelerated in the presence of phenobarbitone due to induction of its metabolism. Clearance of the drug is higher in children, who have greater renal elimination mechanisms. With increased age, the volume of distribution of the drug decreases, total plasma clearance decreases as a function of decreasing renal clearance, and plasma half-life increases.

Adverse effects of cimetidine include diarrhea, dizziness, somnolence, reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), gynecomastia, reversible impotence, decrease in white blood cell counts, increase in serum transaminase and mild rash.

Cimetidine is available commercially as Tagamet(R) oral, film-coated tablets, 200, 300, 400 and 800 mg, manufactured by Smith-Kline Beecham. For treatment of active duodenal ulcer, the usual adult oral dosage of cimetidine is 800 mg daily at bedtime. For maintenance therapy following healing of acute duodenal ulcer, the usual oral dosage of cimetidine is 400 mg daily at bedtime. For the treatment of pathologic hypersecretory conditions, the usual adult oral dosage is 300 mg 4 times daily with meals and at bedtime. For the treatment of active benign gastric ulcer, the usual adult oral dosage is 800 mg at bedtime or 300 mg 4 times daily with meals and at bedtime.

The firm has submitted the results of single dose, fasting and post-prandial bioequivalence studies comparing TorPharm's Cimetidine Tablets, 800 mg, with Smith Kline & French's Tagamet^{R} Tablets, 800 mg. The firm has also submitted the comparative dissolution data for the 800, 400, 300 and 200 mg strengths of the above products and requested waiver of in-vivo bioequivalence requirements for the lower

strengths based on in-vitro data as well as formulation proportionality.

II. Bioequivalence Studies:

A. Single-Dose, Fasting Study for the 800 mg Strength: (Study # 090-96-10718)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of TorPharm's Cimetidine Tablets, 800 mg, and Smith Kline & Beecham's Tagamet^{R} Tablets, 800 mg, in a fasting single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at the PharmaKinetics Laboratories, Baltimore, MD, between August 18 and August 27, 1995. The principal investigator was Calvin Fuhrmann, M.D.. Serum samples were assayed by the same facilities under the supervision of between August 28 and September 5, 1995.

Demographics:

Twenty-six normal, healthy male volunteers between 21-58 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two treatment, two period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 129 - 216 lbs and 65 - 78 in., respectively. There were 15 black and 11 caucasian subjects.

Inclusion Criteria:

The subjects especially did not have any history of: peptic or duodenal ulcer disease, diabetes, asthma, mental illness, nervous system disease, or heart, liver, kidney or gastrointestinal diseases, or problems in forming blood cells (hematopoietic disease); hypersensitivity or idiosyncratic reaction to cimetidine or any other histamine H2

receptor antagonists; or alcoholic or drug addiction.

Restrictions:

They were free of all medications at least 14 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol was allowed for 48 hours before and during dosing. No caffeine or xanthine containing products were allowed 24 hours prior to and during each study session. The subjects fasted for 10 hours prior to and 5 hours after each drug administration. The washout duration between the two phases was seven days. Duration of confinement was 12 hours prior to drug administration until at least 16 hours after drug administration for each period.

Treatment and Sampling:

The two treatments consisted of a single 800 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: TorPharm's Cimetidine Tablets, 800 mg, lot # 50043A (Batch size of __ , nits, potency of 98.5%LC).

Reference Product: SKB's Tagamet^{R} Tablets, 800 mg, lot # 804 4T27 (Potency of 100.5%LC)

Blood samples were collected at predose, 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0 and 16.0 hours following drug administration. The serum was separated, transferred to labelled tubes, and promptly frozen at -20^{0}C for analysis.

Assay Methodology:

The analytical method was developed PharmaKinetics Laboratories. Cimetidine was

[illegible] using an organic solvent.

Assay Specificity:

The assay was specific for cimetidine with no significant interferences seen at the retention time of the drug in [illegible] of predose samples or blank plasma standards.

Linearity: **(Based on actual study standard curves)**

The assay was linear in the range of 0.100 mcg/ml to 10.0 mcg/ml.

Reproducibility: **(Based on actual study QC's)**

Interday CV's were: 6.04 % at 0.250 mcg/ml, 2.92 % at 1.00 mcg/ml, and 3.20 % at 5.00 mcg/ml.

Sensitivity: **(Based on actual study standard data)**

Sensitivity limit was 0.100 mcg/ml (CV% = 1.04). Any level below these limits were reported as zero.

Pre-study validation data showed CV% for 0.100 mcg/ml as QC was 4.33 (n=5).

Accuracy: **(Based on actual study QC's)**

Percents of recovery of control samples were: 93.7 % at 0.250 mcg/ml, 92.4 % at 1.00 mcg/ml, and 96.8 % at 5.00 mcg/ml.

Stability:

Long-term stability: Cimetidine was shown to be stable at -20^{0}C for a 18 day period which covers both the clinical and analytical portions of the study.

Freeze-thaw stability (3 cycles), room-temperature stability (24 hours), and autosampler stability (32 hours) were demonstrated and found acceptable.

Pharmacokinetic Results:

Statistical Analyses:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX, $CMAX_{first\ peak}$, TMAX and $TMAX_{first\ peak}$ were observed values of the highest peak concentration, the first peak concentration of the double-peak phenomenon (where applicable), time to CMAX and time to $CMAX_{first\ peak}$, respectively. KEL and T1/2 were extrapolated and calculated from the terminal portion of the concentration log versus time curve.

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatments, subjects within sequence, and days of administration for the above pharmacokinetic parameters, lnAUC(0-T), lnAUC(0-Infinity) and lnCMAXs. The 90% confidence intervals for AUC's, lnAUC's, CMAXs and lnCMAXs were calculated , based on least squares means, using the two, one-sided t-test.

Results:

Twenty-five of twenty-six enrolled volunteers completed the clinical portion of the study. Subject #13 withdrew voluntarily after completing Period 1. The statistical analysis was performed using 25 data sets.

There was no significant difference (alpha=0.05) between treatments for all parameters analyzed. The results are summarized in the tables below:

Table I

Cimetidine Comparative Pharmacokinetic Parameters
Fasting Study of the 800 mg Strength
Dose = 800 mg; n = 25

Parameters	TorPharm's Mean (CV)	Tagamet^{R} Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) mcg.hr/ml	17.66*	18.53*	[0.91;1.00]	0.95
AUC (0-Inf) mcg.hr/ml	18.19*	19.02*	[0.92;1.00]	0.96
CMAX mcg/ml	4.03*	4.60*	[0.87;1.00]	0.93
$CMAX_{first}$ mcg/ml	3.69*	3.94*	[0.85;1.03]	0.94
TMAX (hrs)	2.20(49)	1.87(44)		
$TMAX_{first}$ (hrs)	1.51(70)	1.24(40)		
KEL (1/hrs)	0.270(15)	0.276(13)		
T1/2 (hrs)	2.63(18)	2.55(13)		

*Geometric LS Means

Table II
Comparative Mean Serum Levels of Cimetidine
mcg/ml(CV)
Fasting Study of the 800 mg Strength
Dose = 800 mg; n = 25

Hour	TorPharm's	Tagamet^{R}
0	0	0
0.25	0.138(152)	0.134(228)
0.50	1.22 (77)	1.53 (76)
0.75	2.30 (56)	2.82 (56)
1.00	2.98 (50)	3.25 (47)
1.33	3.43 (44)	3.54 (47)
1.67	3.59 (41)	3.64 (36)
2.00	3.57 (38)	3.78 (31)
2.50	3.36 (38)	3.65 (25)
3.00	3.05 (37)	3.34 (24)
3.50	2.73 (29)	2.87 (23)
4.00	2.28 (28)	2.47 (27)
5.00	1.68 (26)	1.73 (23)
6.00	1.23 (33)	1.21 (24)
7.00	0.88 (32)	0.86 (22)
8.00	0.66 (31)	0.63 (23)
10.00	0.39 (33)	0.38 (26)
12.00	0.22 (36)	0.21 (37)
14.00	0.11 (75)	0.11 (64)
16.00	0.038(169)	0.030(184)
$AUC(0\text{-}T)_{mcg.hr/ml}$	18.07(22)	18.91(20)
$AUC(0\text{-}I)_{mcg.hr/ml}$	18.59(21)	19.39(20)
CMAX	4.50 (30)	4.77 (29)
$CMAX_{first}$	3.97 (37)	4.26 (40)

Adverse Effects:

Four mild adverse events were reported.

B. Single-Dose, Post-Prandial Study for the 800 mg Strength: (Study # 090-97-10719)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of TorPharm's Cimetidine Tablets, 800 mg, and Smith Kline & Beecham's Tagamet^{R} Tablets, 800 mg, in a post-prandial, single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at the PharmaKinetics Laboratories, Baltimore, MD, between August 23 and August 31, 1995. The principal investigator was Calvin Fuhrmann, M.D. Serum samples were assayed by the same facilities under the supervision of .o between September 5 and September 14, 1995.

Demographics/Inclusion Criteria:

Twenty-six normal, healthy male volunteers between 20-45 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two treatment, two period, randomized crossover study. The selection and exclusion criteria and the restrictions are the same as in the fasting study above. The subjects' weight and height ranged 129 - 192 lbs and 66 - 77 in, respectively.

Restrictions:

The subjects fasted for 10 hours and then were given a standardized breakfast approximately 35 minutes prior to the drug administration. The standardized breakfast consisted of one fried egg, 1 slice of Canadian bacon, 1 slice of American cheese, 1 buttered English muffin, 1 serving of hashed brown potatoes, 180 ml of orange juice and 240 ml of whole milk. The washout duration between two phases was 7 days. Duration of confinement was 12 hours prior to drug administration until

approximately 16 hours post-dose for each period.

Treatment and Sampling:

The two treatments were the same as given in the protocol #090-96-10718 above. Blood samples were collected at predose, 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0 and 16.0 hours following drug administration.

Assay Methodology:

Same analytical method as that used in the fasting study above.

Assay Specificity:

Acceptable.

Linearity: **(Based on actual study standard curves)**

The assay was linear in the range of 0.100 to 10.00 mcg/ml.

Reproducibility: **(Based on actual study Qcs)**

Interday CV's were: 7.86 % at 0.250 mcg/ml, 3.43 % at 1.00 mcg/ml, and 3.98 % at 5.00 mcg/ml.

Sensitivity: **(Based on back-calculated actual study lowest standard data)**

Sensitivity limit was 100 ng/ml (CV% = 0.79). Any level below these limits were reported as zero.

Accuracy: **(Based on actual study Qcs)**

Percents of recovery of control samples were: 94.9 % at 0.250 mcg/ml, 92.6 % at 1.00 mcg/ml, and 97.0 % at 5.00 mcg/ml.

Stability:

Long-term stability: Cimetidine was shown to be stable at -20°C for a 22 day period which covers both the clinical and analytical portions of the study.

Freeze-thaw stability (3 cycles), room-temperature stability (24 hours), and autosampler stability (32 hours) were demonstrated and found acceptable.

Pharmacokinetic Results:

Statistical Analyses:

Same as in the fasting study above.

Results:

Twenty-five of 26 enrolled volunteers completed the clinical portion of the study. Subject 18 voluntarily withdrew after Period 1. The statistical analysis was performed using 25 data sets.

There were significant differences (alpha=0.05) between treatments for AUC (0-T) (p=0.0101), lnAUC(0-T) (p=0.0057), AUC (0-Infinity)(p=0.0155) and lnAUC(0-I) (p=0.0092). The results are summarized in the tables below:

Table III

Cimetidine Comparative Pharmacokinetic Parameters

Post-Prandial Study of the 800 mg Strength

Dose = 800 mg; n = 25

Parameters	TorPharm's(fed) Mean (CV)	Tagamet^{R}(fed) Mean (CV)	% C.I.	Ratio T/R
AUC (0-T) mcg.hr/ml	16.03*	16.82*	[0.93;0.98]	0.95
AUC (0-Inf) mcg.hr/ml	16.57*	17.36*	[0.93;0.98]	0.95
CMAX mcg/ml	3.80*	3.90*	[0.92;1.03]	0.97
$CMAX_{first}$ mcg/ml	3.76*	3.82*	[0.91;1.07]	0.98
TMAX hrs	2.36(38)	2.41(37)		
$TMAX_{first}$ hrs	2.28(41)	2.29(36)		
KEL (1/hrs)	0.285(16)	0.287(19)		
T1/2 (hrs)	2.50	2.52		

*Geometric LS Means

Table IV
Comparative Mean Serum Levels of Cimetidine
mcg/ml(CV)
Food Study of the 800 mg Strength
Dose = 800 mg; n = 25

Hour	TorPharm's(fed)	Tagamet^{R}(fed)
0	0	0
0.25	0.006(500)	0.005(500)
0.50	0.29 (176)	0.28 (193)
0.75	1.01 (136)	0.86 (148)
1.00	1.81 (99)	1.57 (124)
1.33	2.65 (66)	2.22 (78)
1.67	3.08 (50)	2.86 (59)
2.00	3.13 (42)	3.31 (42)
2.50	3.14 (34)	3.19 (35)
3.00	2.98 (33)	3.06 (31)
3.50	2.57 (29)	2.68 (32)
4.00	2.30 (32)	2.48 (33)
5.00	1.74 (28)	1.90 (34)
6.00	1.26 (29)	1.39 (35)
7.00	0.92 (32)	1.00 (36)
8.00	0.69 (36)	0.78 (44)
10.00	0.39 (39)	0.46 (47)
12.00	0.22 (43)	0.26 (55)
14.00	0.10 (98)	0.13 (86)
16.00	0.029(238)	0.047(180)
$AUC(0\text{-}T)_{mcg.hr/ml}$	16.44(24)	17.27(25)
$AUC(0\text{-}I)_{mcg.hr/ml}$	16.99(24)	17.82 (25)
CMAX	3.96 (29)	4.10 (33)
$CMAX_{first}$	3.94 (30)	4.02 (34)

Adverse Effects:

Four mild adverse events were reported and considered by the investigator to be not related to the drug administration.

III. Dissolution Testing:

The dissolution testing was not conducted according to the FDA-approved and current compendial specifications. The dissolution medium should be water instead of 0.1N HCl as used by the firm.

IV. Comments:

1. The single-dose fasting and fed bioequivalence studies for the 800 mg strength demonstrate that the test and reference products are equivalent in their rate and extent of absorption as measured by lnCMAX, lnAUC (0-T) and lnAUC (0-Infinity) of Cimetidine.

2. Comparative formulations given for 200 mg, 300 mg, 400 mg and 800 mg (attached) show that three lower strengths are proportionally similar to the 800 mg.

V. Deficiency:

The dissolution data for the 200 mg, 300 mg, 400 mg and 800 mg strengths of the test product are not acceptable due to the incorrect medium used. According to the FDA-approved and current compendial specifications, the dissolution medium should be water instead of 0.1N H Cl as used by the firm.

VI. Recommendations:

1. The in-vitro dissolution testing conducted by TorPharm on its Cimetidine Tablets, 200 mg, 300 mg, 400 mg and 800 mg, has been found unacceptable.

The dissolution testing should be in according to the FDA-approved and current compendial specifications. The dissolution testing should be conducted in 900 ml of water at 37C using USP XXIII apparatus I(basket) at 100 rpm. The test product should meet the following specifications:

dissolved in 15 minutes.

The waiver request for the lower strengths can not be granted due to the deficiency in dissolution testing.

2. The single-dose fasting and fed bioequivalence studies conducted by TorPharm Inc. on the test product, Cimetidine Tablets, 800 mg, lot # 50043, comparing it with the reference product, Smith Kline Beecham's Tagamet[R] Tablets, 800 mg, lot # 8044T27, have been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product is bioequivalent to the reference product under fasting and fed conditions. The application is, however, incomplete pending acceptable dissolution data.

The firm should be informed of the Deficiency above.

8-14-96

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 8/15/96

Concur: _____ Date: 8/16/96

Keith Chan, Ph.D.
Director, Division of Bioequivalence

WF # 748905dw. 496 Attachment 1 of 5

Components and Composition Continued...

2. Statement of Composition:

Page(s) 3

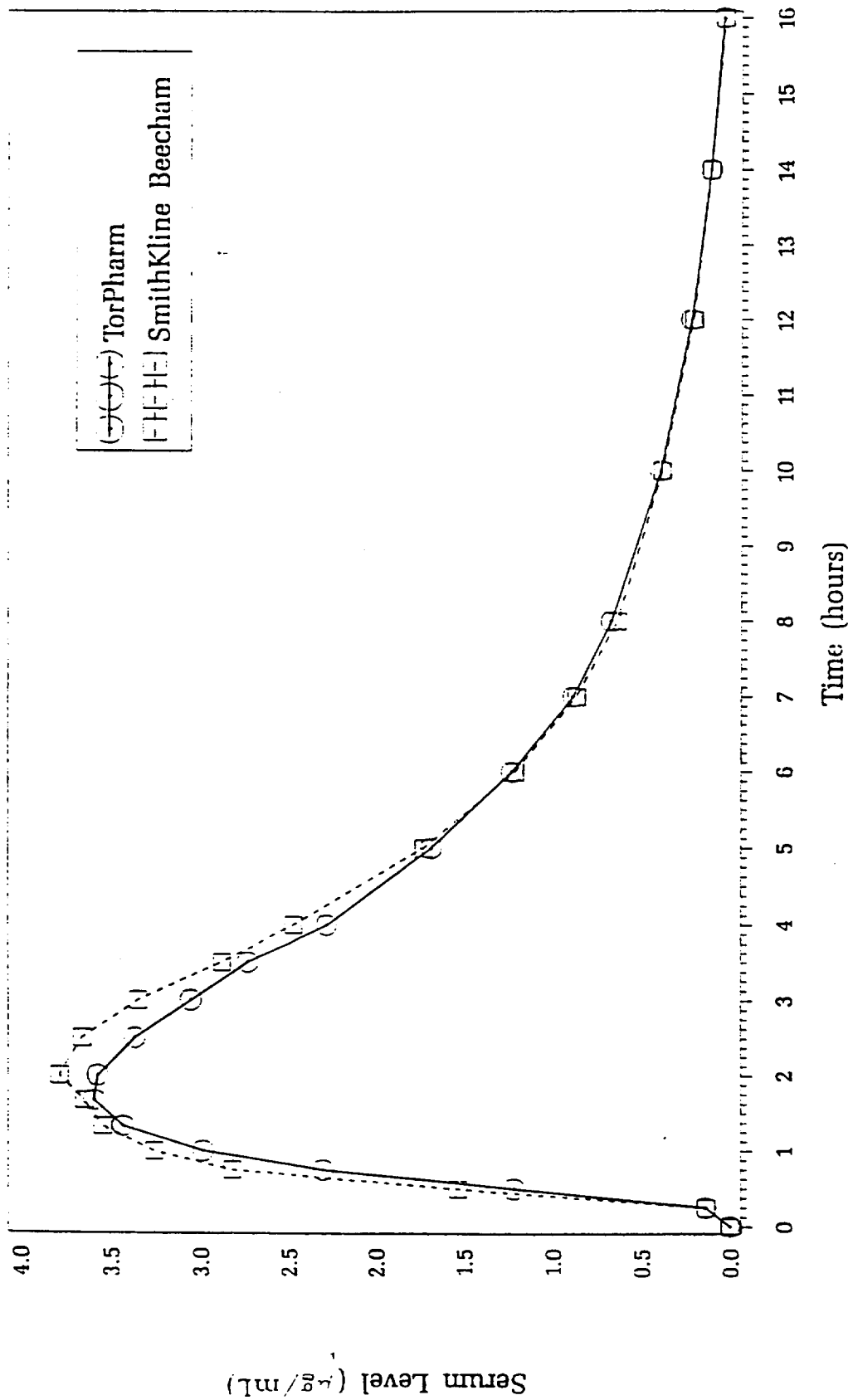
Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Composition

Figure 1: Mean Cimetidine Serum Levels

#090 – 96 – 10718

N = 25



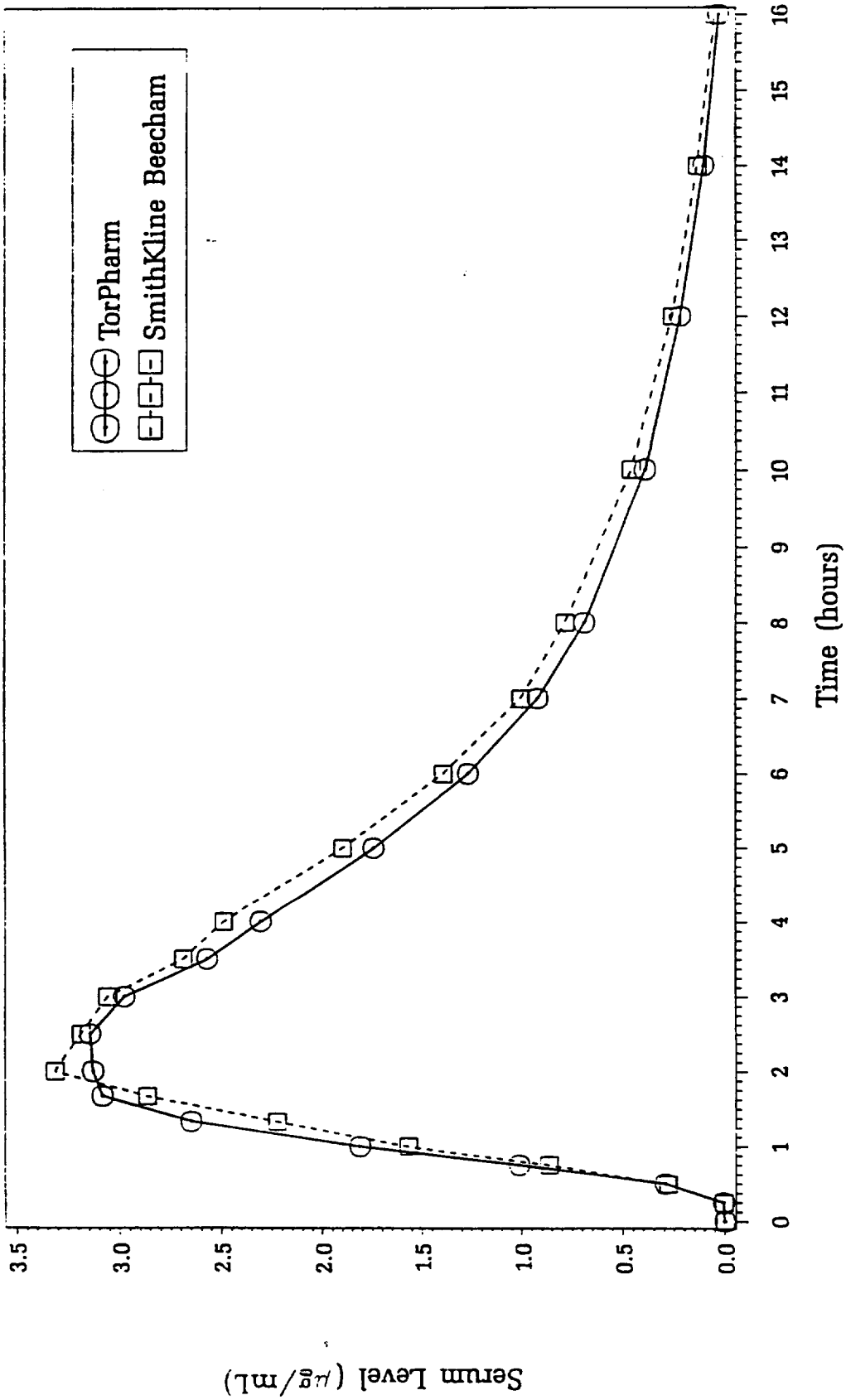


Figure 1: Mean Cimetidine Serum Levels
#090-97-10719
N = 25

Figure 1: Mean Cimetidine Serum Levels

#090-96-10718

N = 25

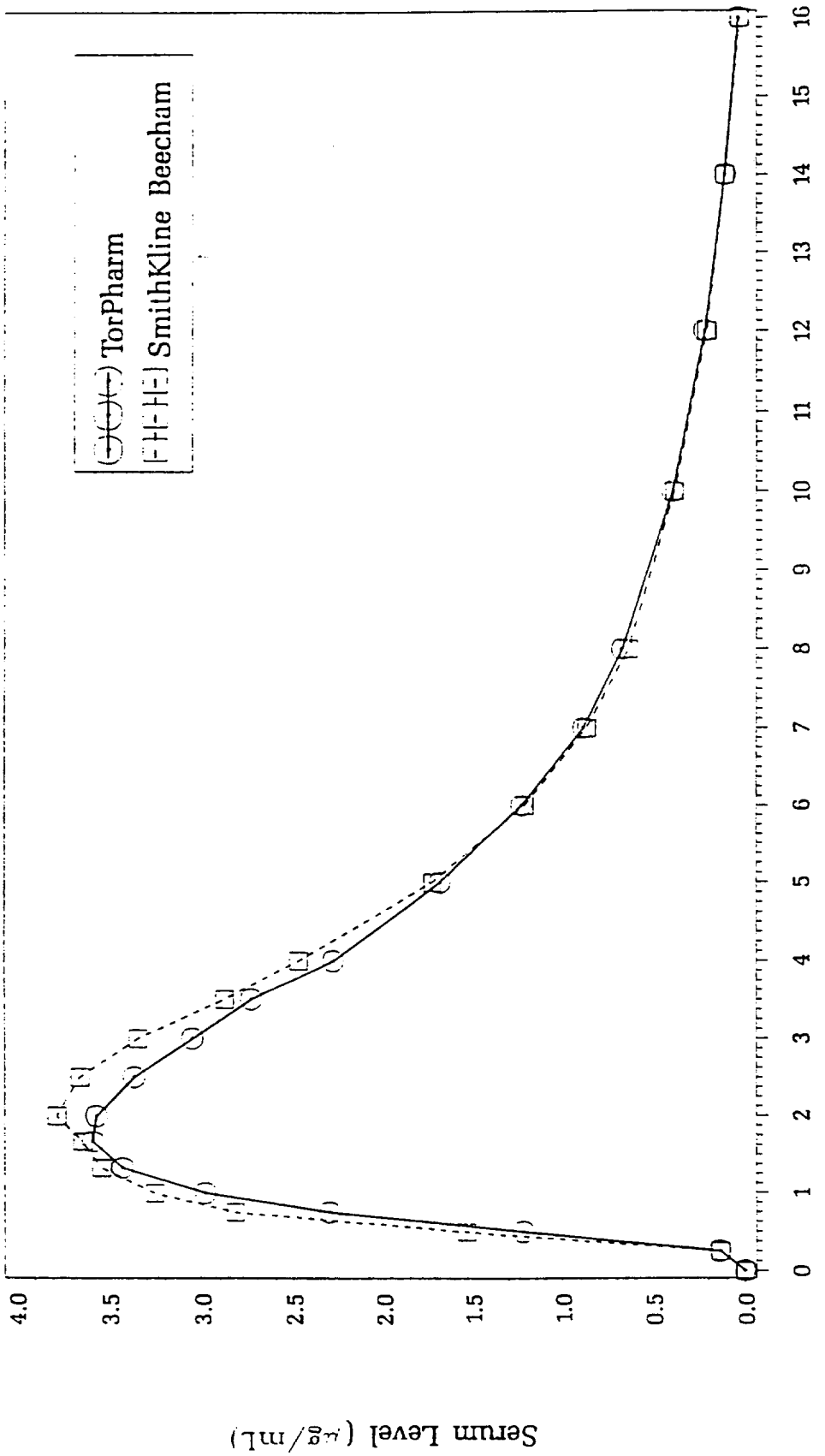


Figure 1: Mean Cimetidine Serum Levels

#090-97-10719

N = 25